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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,343	01/30/2006	Andrzej Lipkowski	7444/73871/GJG	4648

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EXAMINER
HA, JULIE

ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
07/06/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,343	LIPKOWSKI ET AL.	
	Examiner	Art Unit	
	JULIE HA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,5-9 and 11-23* is/are pending in the application.

4a) Of the above claim(s) *11-16 and 18-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-3,5-9,17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Non-final office action filed on April 6, 2009 is acknowledged. Claims 2-3, 5-9, 11-23 are pending in this application. Applicant elected with traverse Group I, and elected species $(Tyr\text{-}D\text{-}Met\text{-}Gly\text{-}Phe\text{-}NH)_2$ on April 9, 2007. Applicant's arguments were not found persuasive and restriction requirement was deemed proper and made FINAL in the previous office action mailed on June 26, 2007, and maintained throughout the prosecution. Claims 11-16 and 18-23 remain withdrawn from further consideration, as being drawn to nonelected invention and species. Claims 2-3, 5-9 and 17 are examined on the merits in this office action.

1. This application contains claims 11-16 and 18-23 drawn to an invention nonelected with traverse in the reply filed on April 9, 2007. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

37 CFR 1.132 Declaration

2. The declaration under 37 CFR 1.132 filed April 6, 2009 is insufficient to overcome the rejection of claims 2-3, 6-8 and 17 and claims 2-3, 5-9 and 17 based upon 35 U.S.C. 103(a) as set forth in the last Office action because: the declaration filed does not disclose what the duration is for each monomers tested, and what is considered "comparable". For example, the declaration indicates that "Tyr-D-Met-Gly-Phe-NH_2 and Tyr-D-Ala-Gly-Phe-NH_2 were found to be comparable for the same dosage tested", but no data is given to compare what the anti-nociception is for the Tyr-

D-Ala-Gly-Phe-NH_2 monomer at 30 minutes and 60 minutes relative to Tyr-D-Met-Gly-Phe-NH_2 monomer.

Maintained Rejection

35 U.S.C. 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 2-3, 6-8 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ronai et al (Biochem. Biophys. Res. Comm., 1979, 91: 1239-49) in view of Abbruscato et al (J. Neurochem., 1997, 69: 1236-45) and Kanai et al (J. Biol. Chem., 1998, 273: 23629-32).

7. Ronai et al teach the tetrapeptide-amide analog of enkephalin H-Tyr-D-Met-Gly-Phe-NH_2 and its opioid activity in guinea pig ileum (abstract). The difference between the reference and the instant claims is that the reference does not teach the elected species (Tyr-D-Met-Gly-Phe-NH-)$_2$.

8. However, Abbruscato et al teach the compound biphalin, (Tyr-D-Ala-Gly-Phe-NH-)$_2$, an opioid peptide containing two pharmocophores linked by a hydrazine bridge. When administered intracerebroventricularly, biphalin has been shown to be more potent than morphine and capable of crossing the blood-brain barrier (see abstract). Abbruscato et al attribute this potency in part to the affinity of the large neutral amino acid carrier for biphalin (see p. 1244, first column). Kanai et al teach that the large neutral amino acid carrier has affinity for methionine (see p. 23629, second column).

9. Therefore, it would have been obvious to one of ordinary skill in the art to substitute methionine for the alanine in biphalin taught by Abbruscato et al in order to mimic the tetrapeptide taught by Ronai et al, satisfying all of the limitations of claim 2. With respect to claim3, Abbruscato et al teach biphalin in combination with pharmacologically acceptable carrier, in the form of an aqueous saline solution, and

formulated for direct application to the site of analgesic activity including the CNS (see p. 1237). The skilled artisan would have been motivated to make this substitution given that the large neutral amino acid carrier has a greater affinity for methionine than alanine and that the affinity of this receptor for biphalin is responsible in part for biphalin's potency. There would have been reasonable expectation of success given that the tetrapeptide harboring methionine instead of alanine has opioid activity. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Applicant's Arguments

10. Applicant notes that "the claimed dimer shows an unexpectedly long duration of anti-nociception over biphalin disclosed in the cited art. In support of this assertion, applicants attach hereto as Exhibit 1 a DECLARATION UNDER 37 CFR 1.132 of ANDRZEJ W. LIPKOWSKI." Applicant argues that "the attached declaration of anti-nociception achieved by the claimed dimer could not have been predicted by one of ordinary skill in the art based on the duration of anti-nociception elicited by biphalin versus the "biphalin monomer". Applicant argues that "while the monomers Tyr-D-Ala-Gly-Phe-NH_2, and Tyr-D-Met-Gly-Phe-NH_2 show comparable duration of anti-nociception, biphalin shows 30% anti-nociceptive activity as measured in the rat tail-flick test at 30 minutes after administration and zero anti-nociceptive activity at 120 minutes after administration. Because the duration of the anti-nociception of the monomers is comparable, one would expect the claimed dimer to show a pattern of anti-nociception

similar to that of biphalin. However, at the same dosage as biphalin, the claimed dimer (Tyr-D-Met-Gly-Phe-NH-)$_2$ actually shows 55% anti-nociceptive activity at 30 minutes after administration, and is still eliciting 30% anti-nociceptive activity at 120 minutes after administration."

In the 132 declaration, Applicant declare that "experiments were performed using a rat tail-flick model of anti-nociception to determine the duration of anti-nociception of each of (1) Tyr-D-Met-Gly-Phe-NH_2; (2) (Tyr-D-Met-Gly-Phe-NH-)$_2$; (3) Tyr-D-Ala-Gly-Phe-NH_2; and (4) (Tyr-D-Ala-Gly-Phe-NH-)$_2$." Applicant indicates that "the duration of anti-nociception of the two monomers, namely Tyr-D-Met-Gly-Phe-NH_2 and Tyr-D-Ala-Gly-Phe-NH_2, to be comparable for the same dosage tested…the level of anti-nociception elicited by 0.005 nmol biphalin, i.e. the dimer (Tyr-D-Ala-Gly-Phe-NH-)$_2$ to be 30% maximum possible effect (MPE) at 30 minutes after administration and equivalent to 0% MPE at 120 minutes after administration…the level of anti-nociception elicited by 0.005 nmol of the dimer (Tyr-D-Met-Gly-Phe-NH-)$_2$ to be 55% MPE at 30 minutes after administration of the dimer and 30% MPE at 120 minutes after administration."

11. Applicant's arguments have been fully considered but have not been found persuasive because Ronai et al teach the monomer of Tyr-D-Met-Gly-Phe-NH_2 and Abbruscato et al teach the compound biphalin (Tyr-D-Ala-Gly-Phe-NH-)$_2$ and has shown that biphalin has been shown to be more potent than morphine and capable of crossing the BBB.

In regards to Applicant's 132 declaration, Applicant compares the of Tyr-D-Met-Gly-Phe-NH_2 and Tyr-D-Ala-Gly-Phe-NH_2, and indicate that at the same dosage range, the anti-nociception was comparable. However, no data is provided to indicate what is meant by "comparable". Since comparable is a relative term, it is hard to determine what anti-nociception level is considered to be comparable. Exhibit A discloses the comparison of Tyr-D-Met-Gly-Phe-NH_2 and (Tyr-D-Met-Gly-Phe-NH-)$_2$ anti-nociception level. The monomer had a the % MPE levels of about 60% (at 5 minutes), about 82% (at 15 minutes), about 40% (at 30 minutes), about 12% (at 60 minutes) and -10% (at 120 minutes). The dimer has a % MPE levels of about 40% (at 5 minutes), about 74% (at 15 minutes), about 55% (at 30 minutes), about 35% (at 60 minutes) and about 30% (at 120 minutes). So what % MPE of D-Ala monomer is considered to be comparable to the D-Met monomer? If the D-Ala monomer had lower initial % MPE than the D-Met monomer, then the D-Ala dimer would be expected to have lower % MPE than the D-Met dimer. Furthermore, it is hard to determine at what time frame the anti-nociception levels were comparable. One would expect that at initial time point, the activity would be comparable. Therefore, until a data comparing the D-Ala monomer relative to D-Met monomer is provided, and the D-Ala monomer activity is compared to the D-Met monomer activity, the unexpected results of D-Met dimer having a greater duration of anti-nociception is not convincing.

Therefore, as set forth in the previous office action, the prior arts combined are prima facie obvious over the instant claims 2-3, 6-8 and 17.

12. Claims 2-3, 5-9 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ronai et al (Biochem. Biophys. Res. Comm., 1979, 91: 1239-49), Abbruscato et al (J. Neurochem., 1997, 69: 1236-45) and Kanai et al (J. Biol. Chem., 1998, 273: 23629-32) as applied to claims 2-3 and 6-8 above in further view of Hill (US Patent # 5880132), Bock et al (EP 0434369 A1) and Ornstein (US Patent # 5356902).

13. Ronai et al, Abbruscato et al and Kanai et al do not teach the administration of (Tyr-D-Met-Gly-Phe-NH-)$_2$ in combination with compounds that block stimulatory amino acid, tachykinin or cholecystokinin receptors (claim 5) or in combination with biphalin.

14. Ornstein teaches stimulatory amino acid antagonists, decahydroisoquinoline compounds, and their use as analgesic compounds (column 2, lines 6 and 7). Hill teaches pharmaceutical compositions comprising both piperidine tachykinin antagonist and opioid analgesics (abstract). Bock et al teach cholecytokinin antagonists and their ability to potentiate morphine and other analgesics.

15. Therefore, it would have been obvious to one of ordinary skill in the art to combine the (Tyr-D-Met-Gly-Phe-NH-)$_2$ analgesic taught by combination of Ronai et al, Abbruscato et al and Kanai et al and the stimulatory amino acid, tachykinin or cholecystokinin receptor antagonists taught by Ornstein, Hill and Bock et al or the biphalin taught by Abbruscato et al. The skilled artisan would have been motivated to do so given that the prior art teaches that compounds such as (Tyr-D-Met-Gly-Phe-NH-)$_2$ and biphalin have the same or complimentary functions as stimulatory amino acid, tachykinin or cholecystokinin receptor antagonists. There would have been a reasonable expectation of success given that the stimulatory amino acid, tachykinin or

cholecystokinin receptor antagonists and their pharmaceutical use are well-known in the prior art and compatible with opioid analgesics. The MPEP states in section 2144.06: "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose...[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980)" Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Applicant's Arguments

16. Applicant notes that "the claimed dimer shows an unexpectedly long duration of anti-nociception over biphalin disclosed in the cited art. In support of this assertion, applicants attach hereto as Exhibit 1 a DECLARATION UNDER 37 CFR 1.132 of ANDRZEJ W. LIPKOWSKI." Applicant argues that "the attached declaration of anti-nociception achieved by the claimed dimer could not have been predicted by one of ordinary skill in the art based on the duration of anti-nociception elicited by biphalin versus the "biphalin monomer". Applicant argues that "while the monomers Tyr-D-Ala-Gly-Phe-NH_2, and Tyr-D-Met-Gly-Phe-NH_2 show comparable duration of anti-nociception, biphalin shows 30% anti-nociceptive activity as measured in the rat tail-flick test at 30 minutes after administration and zero anti-nociceptive activity at 120 minutes after administration. Because the duration of the anti-nociception of the monomers is comparable, one would expect the claimed dimer to show a pattern of anti-nociception

similar to that of biphalin. However, at the same dosage as biphalin, the claimed dimer (Tyr-D-Met-Gly-Phe-NH-)$_2$ actually shows 55% anti-nociceptive activity at 30 minutes after administration, and is still eliciting 30% anti-nociceptive activity at 120 minutes after administration."

In the 132 declaration, Applicant declare that "experiments were performed using a rat tail-flick model of anti-nociception to determine the duration of anti-nociception of each of (1) Tyr-D-Met-Gly-Phe-NH_2; (2) (Tyr-D-Met-Gly-Phe-NH-)$_2$; (3) Tyr-D-Ala-Gly-Phe-NH_2; and (4) (Tyr-D-Ala-Gly-Phe-NH-)$_2$." Applicant indicates that "the duration of anti-nociception of the two monomers, namely Tyr-D-Met-Gly-Phe-NH_2 and Tyr-D-Ala-Gly-Phe-NH_2, to be comparable for the same dosage tested…the level of anti-nociception elicited by 0.005 nmol biphalin, i.e. the dimer (Tyr-D-Ala-Gly-Phe-NH-)$_2$ to be 30% maximum possible effect (MPE) at 30 minutes after administration and equivalent to 0% MPE at 120 minutes after administration…the level of anti-nociception elicited by 0.005 nmol of the dimer (Tyr-D-Met-Gly-Phe-NH-)$_2$ to be 55% MPE at 30 minutes after administration of the dimer and 30% MPE at 120 minutes after administration."

17. Applicant's arguments have been fully considered but have not been found persuasive because the prior arts combined teach or suggest Applicant's invention.

In regards to Applicant's 132 declaration, Applicant compares the of Tyr-D-Met-Gly-Phe-NH_2 (D-Met monomer) and Tyr-D-Ala-Gly-Phe-NH_2 (D-Ala monomer), and indicate that at the same dosage range, the anti-nociception was comparable. However, no data is provided to indicate what is meant by "comparable". Since comparable is a

relative term, it is hard to determine what anti-nociception level is considered to be comparable. Exhibit A discloses the comparison of Tyr-D-Met-Gly-Phe-NH_2 and (Tyr-D-Met-Gly-Phe-NH-)$_2$ anti-nociception level. The monomer had a the % MPE levels of about 60% (at 5 minutes), about 82% (at 15 minutes), about 40% (at 30 minutes), about 12% (at 60 minutes) and -10% (at 120 minutes). The dimer has a % MPE levels of about 40% (at 5 minutes), about 74% (at 15 minutes), about 55% (at 30 minutes), about 35% (at 60 minutes) and about 30% (at 120 minutes). So what % MPE of D-Ala monomer is considered to be comparable to the D-Met monomer? If the D-Ala monomer had lower initial % MPE than the D-Met monomer, then the D-Ala dimer would be expected to have lower % MPE than the D-Met dimer. Furthermore, it is hard to determine at what time frame the anti-nociception levels were comparable. One would expect that at initial time point, the activity would be comparable. Therefore, until a data comparing the D-Ala monomer relative to D-Met monomer is provided, and the D-Ala monomer activity is compared to the D-Met monomer activity, the unexpected results of D-Met dimer having a greater duration of anti-nociception is not convincing. Therefore, as set forth in the previous office action, the prior arts combined are prima facie obvious over the instant claims 2-3, 5-9 and 17.

Conclusion

18. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). No claim is allowed.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Julie Ha/
Examiner, Art Unit 1654

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654